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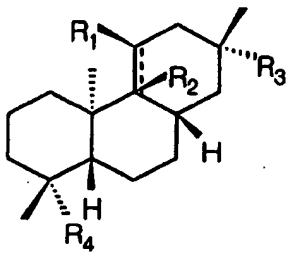

(1)

(57) Abstract

The present invention relates to diterpene derivatives prepared from the components which are extracted from Acanthopanax Koreanum and represented by Chemical Formula (1).

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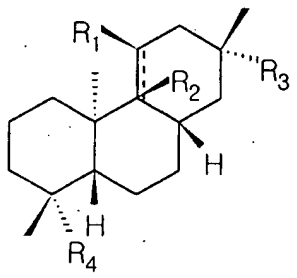
DITERPENE DERIVATIVES AND ANTI-INFLAMMATORY ANALGESIC AGENTS COMPRISING THE SAME

Technical Field

The present invention relates to diterpene derivatives and anti-inflammatory analgesic agents comprising the same. More specifically, the present invention relates to diterpene derivatives prepared from the components which are extracted from Acanthopanax Koreanum and represented by Chemical Formula 1:



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wherein, R_1 and R_2 individually represent hydrogen or hydroxy, or they form a double bond in the cycle, R_3 represents vinyl, hydroxyethyl, methoxyethyl, acetyloxyethyl, methoxymethoxyethyl, methoxyethoxymethoxyethyl, methoxyiminoethyl or isoxazolinyl group, R_4 represents hydroxymethyl, carboxyl, carboxymethyl, carboxyvinyl, carboxyethyl, carboxypropyl, carboxybutyl, carboxybutadienyl, carboxyallyl, carboxyhomoallyl, carbamoyl, methylcarbamoyl, hydroxycarbamoyl, carbazoyl, N-pipsylcarbamoylmethyl, N-pipsylcarbamoylethyl, N-pipsylcarbamoylbutadienyl or N-methanesulfonylcarbamoylethyl group;
and anti-inflammatory analgesic agents comprising the same.

Background Art

Acanthopanax Koreanum is a special product which grows spontaneously in Cheju-do in the Republic of Korea. It is a deciduous shrub belonging to the family of Japanese angelica tree, and taking-out of

the tree from Cheju-do is restricted. The bark of the tree and bark of the root have been known to have effective analgesic action on pain of bones and sinews from ancient times in the field of Chinese medicines. Among the people, wine was made from the bark or root-bark of Acanthopanax Koreanum, and the wine has been used for treatment of neuralgia, paralysis, hypertension and rheumatism.

Recently, the present inventors found the fact that (-)-pimara-9(11),15-diene-4-carboxylic acid among the diterpene components extracted from root-bark and bark of Acanthopanax Koreanum, and novel derivatives synthesized therefrom inhibits the stage where arachidonic acid is converted to PGE_2, an inflammation mediator, thereby having excellent anti-inflammatory action, and the discovery was filed as a patent application (Korean Patent No. 112194).

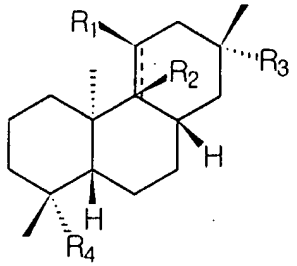
Disclosure of the Invention

The present inventors have continuously performed intensive studies in order to discover an excellent inhibitor against production of PGE_2(prostaglandin E_2), and as a result, could additionally develop a compound having more excellent anti-inflammatory action, and complete the present invention.

The object of the present invention is to provide diterpene derivatives represented by Chemical Formula 1.

Another object of the present invention is to provide an anti-inflammatory analgesic agent comprising the diterpene derivative represented by Chemical Formula 1.

The present invention relates to diterpene derivatives represented by Chemical Formula 1 and anti-inflammatory analgesic agents comprising the same.



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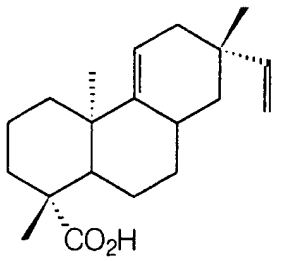
wherein, R_1, R_2, R_3 and R_4 are the same as defined previously.

The compound of Chemical Formula 1 is prepared from the components extracted from Acanthopanax Koreanum, and the process for preparation is described in detail here-in-below:

First, root-bark and bark of Acanthopanax Koreanum is cut into pieces and the pieces are heat-extracted with alcohol in a water bath, and the extract is filtered. After concentrating the combined filtrate of the alcohol extract, water is added, and the mixture is extracted with diethyl ether. The ether extract is concentrated to dryness, and the residue is fractioned by silica gel column chromatography using a mixture of ethyl acetate and hexane as an eluent, to give (-)-pimara-9(11),15-diene-4-carboxylic acid (R_4=COOH) of Chemical Formula 2, the main component of the fractions. In the description of compounds of Chemical Formulas 2 to 48 below, the definitions of R_1 to R_4 in the parentheses are described in order to show how the substituents R_1 to R_4 of Chemical Formulas 2 to 48 are characteristically altered as compared to Chemical Formula 1.



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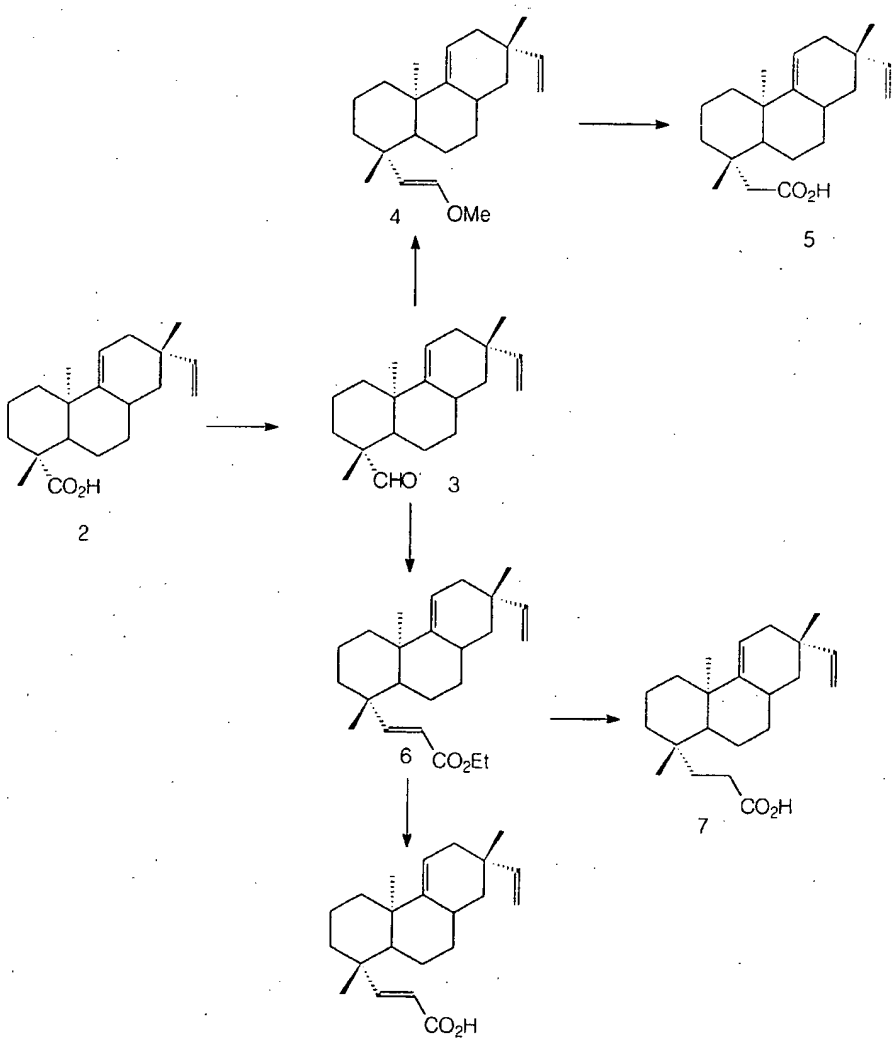
The compound of Chemical Formula 2 is subjected to chemical

reactions shown in Reaction Schemes 1 to 7, to form various derivatives.

Scheme 1

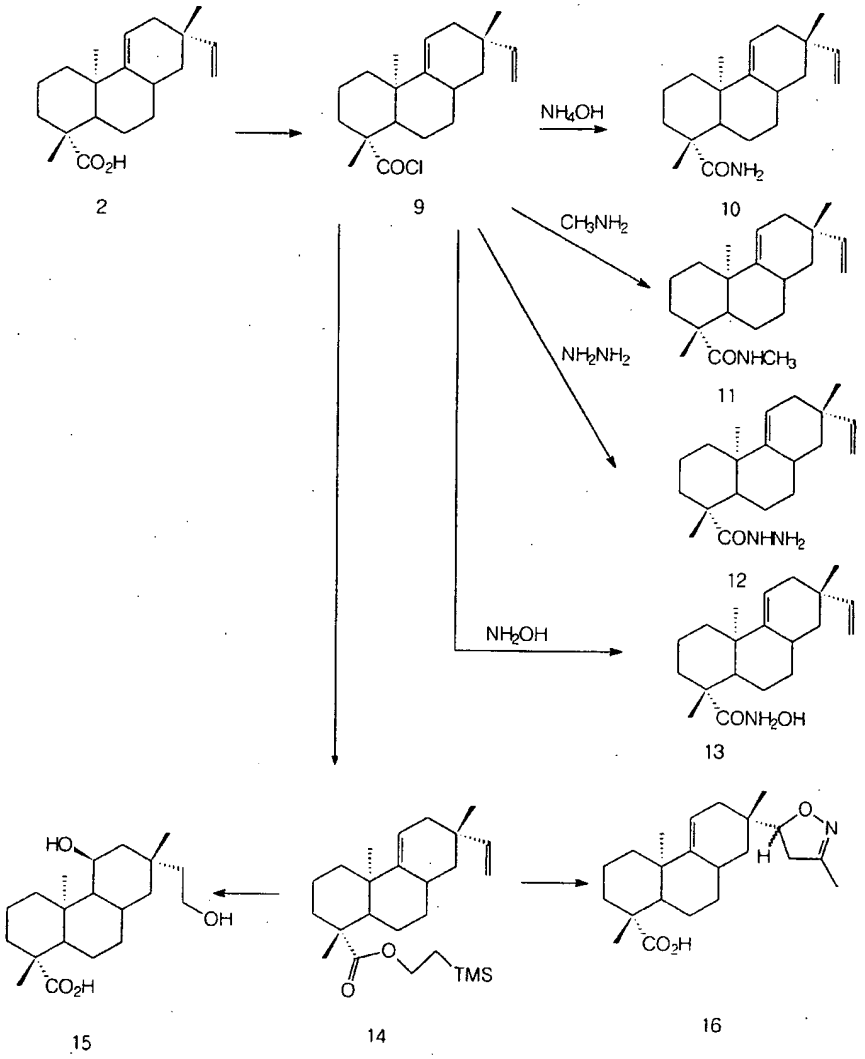


As shown in Reaction Scheme 1, the natural diterpene (R_4=COOH) of Chemical Formula 2 is reduced, and then oxidized, using tetrapropylammonium perruthenate, PDC, PCC or Swern oxidation, to give a compound (R_4=CHO) of Chemical Formula 3. The aldehyde group of the compound of Chemical Formula 3 thus obtained is subjected to Wittig reaction using triethylphosphono acetate anion in tetrahydrofuran to obtain a double bond in the compound of Chemical Formula 6. The double bond of the conjugated ester is reduced by

magnesium in methanol, or directly hydrolyzed with lithium hydroxide to obtain a compound of Chemical Formula 7 (R_4=CH_2CH_2COOH) or that of Chemical Formula 8 (R_4=CHCHCOOH). The compound of Chemical Formula 4 (R_4=$CHCHOCH_3$) obtained from Wittig reaction using methoxymethyl phosphorane is hydrolyzed by p-toluenesulfonic acid in acetone to give an aldehyde, which is oxidized by silver oxide in water and ethanol to give a compound of Chemical Formula 5 (R_4=CH_2COOH).

Carbonyl derivatives of the present invention can be prepared according to Reaction Scheme 2 or 3 shown below.

Scheme 2

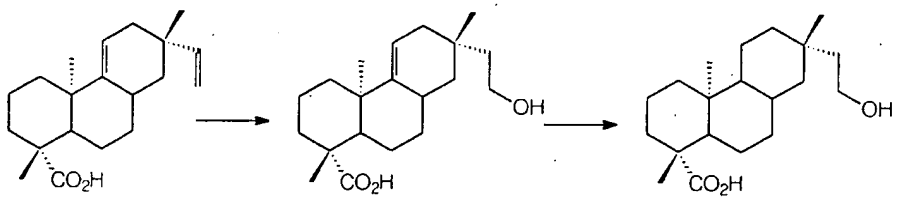


As shown in Reaction Scheme 2, the natural diterpene of Chemical Formula 2 (R_4=COOH) is directly reacted with oxalyl chloride or thionyl chloride in benzene to give a compound of Chemical Formula 9 (R_4=COCl), which is reacted with aqueous ammonia or aqueous solution of methyl amine in ethyl acetate, with hydroxylamine hydrochloride in benzene, or with hydrazine monohydrate in dry ether, to give a compound of Chemical Formula 10 (R_4=$CONH_2$), a compound of Chemical Formula 11 (R_4=$CONHCH_3$), a compound of Chemical Formula 12

(R_4=$CONHNH_2$, carbazoyl), and a compound of Chemical Formula 13 (R_4=CONHOH), respectively.

Similarly, the acid chloride group of the compound of Chemical Formula 9 is reacted with trimethylsilyl ethanol in pyridine to give a compound of Chemical Formula 14 (R_4=$COOCH_2CH_2TMS$) wherein the carboxylic group is protected, which is then reacted with two equivalents of borane-methyl sulfide in tetrahydrofuran and deprotected with tetrabutylammonium fluoride in dimethylformamide to give a compound of Chemical Formula 15 (R_1=OH, R_2=H, R_3=CH_2CH_2OH, R_4=CO_2H). Otherwise, the compound of Chemical Formula 14 wherein the carboxylic group is protected (R_4=$COOCH_2CH_2TMS$) is subjected to additional cyclization using nitrile oxide, which was obtained from N-chlorosuccinimide and acetaldoxime, in tetrahydrofuran, and then deprotected with tetrabutylammonium fluoride to give a compound of Chemical Formula 16 (R_1, R_2 = double bond, R_4 = isoxazolinyl).

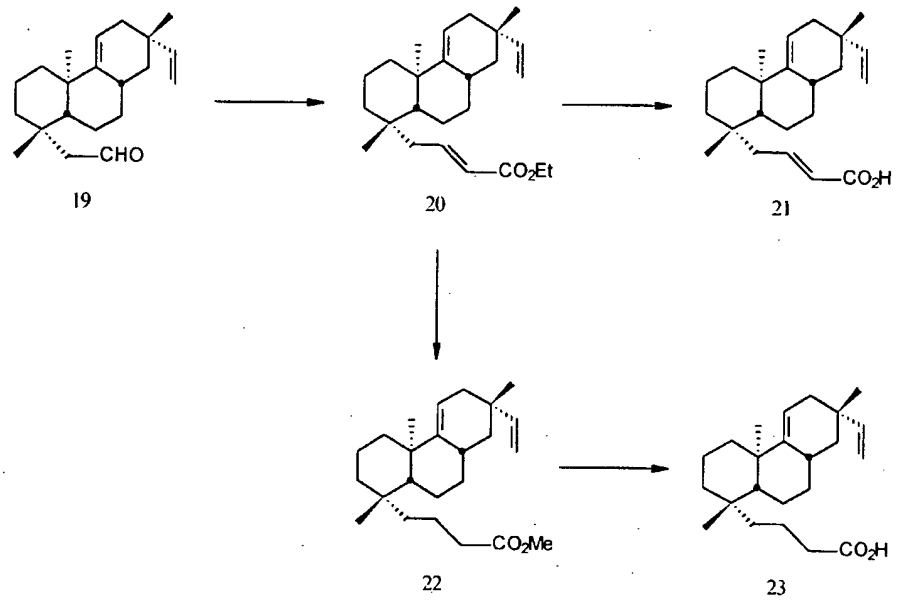
Scheme 3



2 17 18

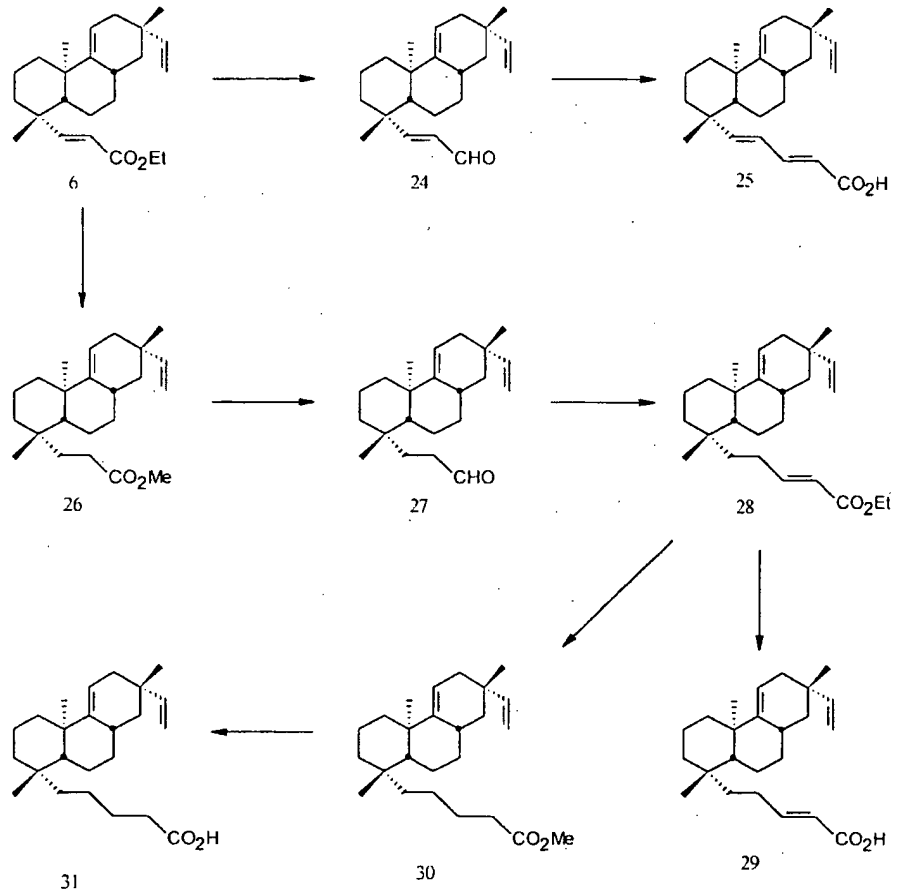
As shown in Reaction Scheme 3 above, the natural diterpene of Chemical Formula 2 (R_4=COOH) is reacted with n-butyllithium in tetrahydrofuran to obtain a carboxylate salt, which is reduced by one equivalent of borane-methyl sulfide complex (BH_3- SMe_2) to give an objective compound of Chemical Formula 17 (R_3=CH_2CH_2OH), without giving any effect on the carboxylic group. The compound of Chemical Formula 17 thus obtained is reduced on contact to give a compound of Chemical Formula 18 (R_1=H_2, R_2=H, R_3=CH_2CH_2OH).

Scheme 4



As shown in Reaction Scheme 4 above, the aldehyde group of the compound of Chemical Formula 19 (R_4=CH_2CHO), which was obtained by hydrolyzing the compound of Chemical Formula 4 as in Reaction Scheme 1, is subjected to Wittig reaction in toluene to obtain a double bond. The conjugated ester is directly hydrolyzed by lithium hydroxide, or reduced by magnesium in methanol and hydrolyzed, to provide a compound of Chemical formula 21 (R_4=$CH_2CHCHCOOH$) or a compound of Chemical Formula 23 (R_4=$CH_2CH_2CH_2COOH$).

Scheme 5



As shown in Reaction Scheme 5 above, the conjugated ester group of the compound of Chemical Formula 6 (R_4=CHCHCO$_2$Et), which was obtained in Reaction Scheme 2, is reduced and then oxidized with tetrapropylammonium perruthenate to provide a compound of Chemical Formula 24 (R_4=CHCHCHO). The aldehyde is subjected to Wittig reaction with triethyl phosphonoacetate anion in tetrahydrofuran to give a diene, which is hydrolyzed with lithium hydroxide to provide a compound of Chemical Formula 25(R_4=CHCHCHCHCO$_2$H).

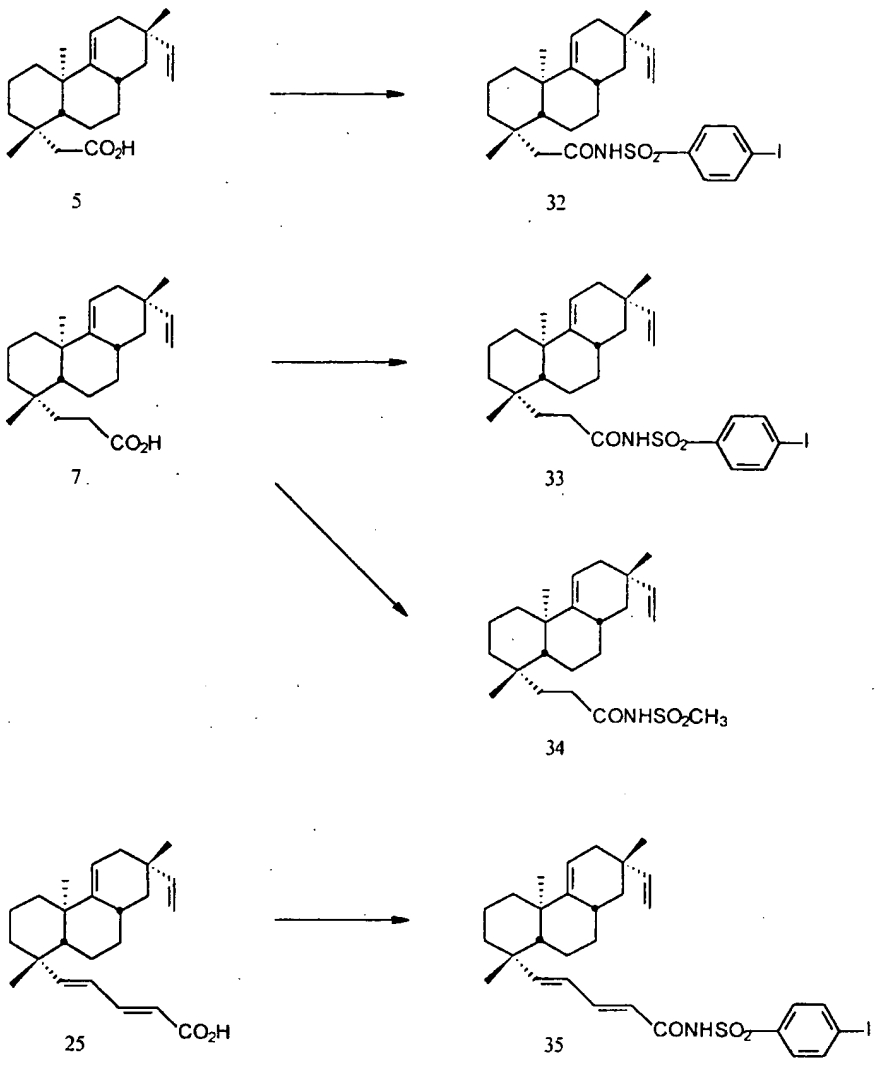
Otherwise, the conjugated ester group of the compound of Chemical Formula 6 (R_4=CHCHCO$_2$Et) is reacted with magnesium in methanol to reduce the double bond and with diisobutylaluminium hydride to reduce the ester group, and then oxidized with

tetrapropylammonium perruthenate to give a compound of Chemical formula 27 (R_4=CH_2CH_2CHO).

The aldehyde group of the compound of Chemical Formula 27 thus obtained is subjected to Wittig reaction using triethyl phosphonoacetate anion in tetrahydrofuran to obtain a double bond, and the double bond of the conjugated ester is directly hydrolyzed with lithium hydroxide, or reduced with magnesium in methanol and hydrolyzed to provide a compound of Chemical Formula 29 (R_4=$CH_2CH_2CHCHCOOH$, carboxyhomoallyl) or a compound of Chemical Formula 31 (R_4=$CH_2CH_2CH_2CH_2COOH$).

The pipsylcarbamoyl derivatives of the present invention can be prepared as shown in Reaction Scheme 6 below.

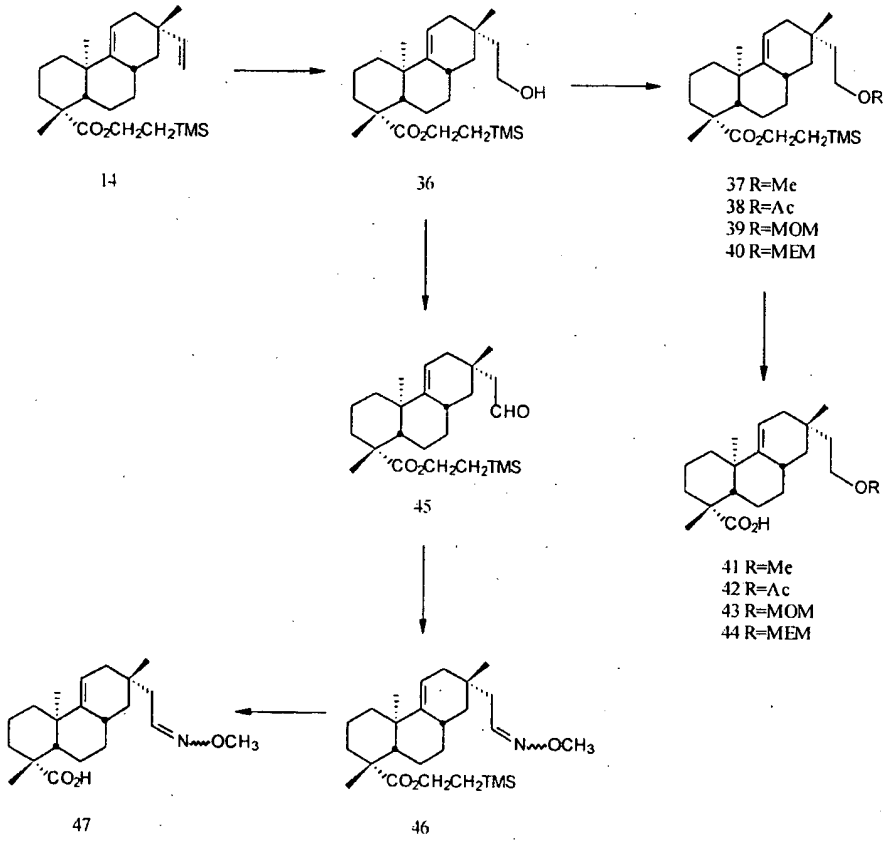
Scheme 6



The carboxylic group of the compound of Chemical Formula 5, 7 or 25 is directly reacted with oxalyl chloride or thionyl chloride in benzene, to give an acid chloride, which is then reacted with pipsylamide anion or methansulfonamide anion obtained by treating pipsylamide or methansulfonamide with sodium hydride in tetrahydrofuran, to give a compound of Chemical Formula 32 (R_4=$CH_2CONHSO_2PhI$, pipsylcarbamoylmethyl), a compound of Chemical Formula 33 (R_4=$CH_2CH_2CONHSO_2PhI$, pipsylcarbamoylethyl), a compound of Chemical Formula 34 (R_4=$CH_2CH_2CONHSO_2CH_3$, methanesulfonylcarbamoylethyl) and a compound of Chemical Formula 35 (R_4=$CHCHCHCHCONHSO_2PhI$, pipsylcarbamoylbutadienyl),

respectively.

Scheme 7



As shown in Reaction Scheme 7 above, the hydroxy group of the compound of Chemical Formula 36 (R_3=CH_2CH_2OH, R_4=$CO_2CH_2CH_2TMS$), which was obtained by reacting the ester of Chemical Formula 14 obtained in Reaction Scheme 3 with 1 equivalent of borane-methyl sulfide, is treated with sodium hydride-iodomethane, acetic anhydride, or methoxymethyl chloride, or methoxyethoxymethyl chloride and deprotected with tetrabutylammonium fluoride in dimethylsulfoxide, to provide a compound of Chemical Formula 41 (R_3=$CH_2CH_2OCH_3$), a compound of Chemical Formula 42 (R_3=CH_2CH_2OAc), a compound of Chemical Formula 43 (R_3=$CH_2CH_2OCH_2OCH_3$) and a compound of Chemical Formula 44 (R_3=$CH_2CH_2OCH_2OCH_2CH_2OCH_3$), respectively.

Meanwhile, the hydroxy group of the compound of Chemical

Formula 36 is oxidized with tetrapropylammonium perruthenate to provide a compound of Chemical Formula 45 (R_3=CH_2CHO), which is condensed with methoxylamine and deprotected with tetrabutylammonium fluoride in dimethylsulfoxide to give a compound of Chemical Formula 47 (R_3=$CH_2CHNOCH_3$).

The dose of the compound represented by Chemical Formula 1 is 0.01 to 1000 mg for an adult per one day as an defined as an anti-inflammatory analgesic agent, and the dose may be conventionally varied depending on age and body weight of the patient as well as the condition of symptoms.

The anti-inflammatory analgesic agent of the present invention may be formulated in proper forms which are suitable for oral administration or parenteral administration, according to the conventional processes for preparing formulations. In case of oral administration, the anti-inflammatory analgesic agent of the present invention may be prepared in the form of a tablet, capsule, solution, syrup, suspension, or the like, while in case of parenteral administration it may be prepared in the form of intraperitoneal, subcutaneous, intramusclar, or transcutaneous injection.

Best Mode for Carrying out the Invention

The present invention is described in more detail with reference to the Examples. It should be noted that the scope of the present invention is not restricted to those Examples.

Example 1 : 4-Hydroxymethyl-(-)-pimara-9(11),15-diene

101mg of (-)-pimara-9(11),15-diene-4-carboxylic acid and 25.4mg of lithium aluminum hydride were dissolved in 3ml of ether and then stirred at room temperature for 10 hours. Some drops of methanol was added thereto to terminate the reaction. 20ml of ether and 20ml of a saturated solution of potassium sodium tartrate tetrahydrate were added to the reaction mixture, which was stirred vigorously at room temperature for 5 hours. The organic layer was washed with water and brine, dried

over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was then purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/5) to afford 82mg of 4-hydroxymethyl-(-)-pimara-9(11),15-diene (85%).

IR(neat) : 3368 cm^{-1}

^{1}H-NMR(300MHz, $CDCl_3$) : 5.75(dd, 1H, J=17.5, 10.7Hz), 5.29(m, 1H), 4.86(dd, 1H, J=17.5, 1.4Hz), 4.79(dd, 1H, J=10.7, 1.4Hz), 3.78(d, 1H, J=10.9Hz), 3.47(d, 1H, J=10.9), 0.84-1.99(m,16H), 0.97(s, 3H), 0.91(s, 3H), 0.90(s, 3H)

Mass(EI) m/e 288(M+)

Example 2 : 4-Formyl-(-)-pimara-9(11),15-diene

55mg of 4-hydroxymethyl-(-)-pimara-9(11),15-diene and catalytic amount of tetrapropylammonium perruthenate, 22.4mg of N-methylmorpholine-N-oxide, and molecular sieve powder were dissolved in 3ml of dichloromethane and then stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure, diluted with diethyl ether, and filtered with silica gel. The filtrate was concentrated under reduced pressure to give a residue, which was then purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 49mg of 4-formyl-(-)-pimara-9(11),15-diene (91%).

IR(neat) : 1717 cm^{-1}

^{1}H-NMR(300MHz, $CDCl_3$) : 9.86(s, 1H), 5.75(dd, 1H, J=17.5, 10.7Hz), 5.33(m, 1H), 4.87(dd, 1H, J=17.4, 1.4Hz), 4.80(dd, 1H, J=10.7, 1.4Hz) 0.86-1.99(m, 16H), 0.96(s, 3H), 0.90(s, 3H), 0.86(s, 3H)

Mass(EI) m/e 286(M+)

Example 3 : 4-Methoxyvinyl-(-)-pimara-9(11),15-diene

To a solution of 23.5mg of (methoxymethyl)triphenylphosphonium chloride in 2ml of tetrahydrofuran, was slowly added a solution of 0.07ml of potassium t-butoxide in tetrahydrofuran (1M). 16.3mg of 4-formyl-(-)-pimara-9(11),15-diene prepared in the above Example 2 was dropwise

added to the reaction mixture, which was then refluxed for 12 hours. The reaction mixture was concentrated under reduced pressure to give a residue, which was diluted with 20ml of ethyl acetate and washed with water and brine. The reaction mixture was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was then purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 19.8mg of 4-methoxyvinyl-(-)-pimara-9(11),15-diene (90%, trans : cis = 2:1).

trans isomer ^{1}H-NMR(300MHz, $CDCl_3$):6.10(d, 1H, J=12.9Hz), 5.75(dd, 1H, J=17.4, 10.7Hz), 5.28(m, 1H), 5.01(d, 1H, J=13.1Hz), 4.86(d, 1H, J=17.3Hz), 4.79(d, 1H, J=10.7Hz), 3.45(s,3H), 0.67-2.23(m, 25H).

cis isomer ^{1}H-NMR(300MHz, $CDCl_3$): 5.75(dd, 1H, J=17.4, 10.7Hz), 5.63(d, 1H, J=7.3Hz), 5.28(m, 1H), 4.86(d, 1H, J=17.3Hz), 4.79(d, 1H, J=10.7Hz), 4.35(d, 1H, J=7.1Hz), 3.44(s,3H), 0.67-2.23(m, 25H)

Example 4 : 4-Formylmethyl-(-)-pimara-9(11),15-diene

7mg of 4-methoxyvinyl-(-)-pimara-9(11),15-diene prepared in the above Example 3 and p-tolunesulfonic acid were dissolved in 2ml of acetone and stirred at 0℃ for 30 minutes. 1ml of a saturated solution of sodium carbonate was added to the reaction mixture, which was then diluted with 20ml of ethyl acetate and washed with water and brine. The reaction mixture was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was then purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/20) to afford 6.2mg of 4-formylmethyl-(-)-pimara-9(11),15-diene (93%).

^{1}H-NMR(300MHz, $CDCl_3$) : 9.79(t, 1H, J=3.4Hz), 5.77(dd, 1H, J=17.4, 10.5Hz), 5.34(m, 1H), 4.86(dd, 1H, J=17.4, 1.4Hz), 4.80(dd, 1H, J=10.6, 1.4Hz), 0.76-2.53(m, 18H), 1.03(s, 3H), 1.01(s, 3H), 0.90(s, 3H)

Example 5 : 4-Carboxymethyl-(-)-pimara-9(11),15-diene

Silver nitrate and sodium hydroxide were dissolved in 2ml of water

and stirred at 0℃ for 1 hour. A solution of 15mg of 4-formylmethyl-(-)-pimara-9(11),15-diene prepared in the above Example 4 in 1ml of ethanol was added the reaction mixture, which was stirred for 9 hours and then filtered. The filtrate was extracted with 20 ml of ethyl acetate. The organic layer was washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was then purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 8mg of 4-carboxymethyl-(-)-pimara-9(11),15-diene (51%).

IR(neat) : 3360(OH), 2923(CH), 1703(CO) cm^{-1}

^{1}H-NMR(300MHz, $CDCl_3$) : 5.74(dd, 1H, J=17.5, 10.7Hz), 5.28(m, 1H), 4.86(dd, 1H, J=17.4, 1.4Hz), 4.80(dd, 1H, J=10.6, 1.4Hz), 2.53(d, 1H, J=12.8Hz), 2.23(d, 1H, J=12.8Hz), 0.61-2.09(m, 16H), 0.99(s, 3H), 0.97(s, 3H), 0.90(s, 3H)

Mass(EI) m/e 316(M+)

Example 6 : 4-Carboethoxyvinyl-(-)-pimara-9(11),15-diene

31.4mg of triethyl phosphonoacetate and 4mg of sodium hydride (60%) were dissolved in 1ml of tetrahydrofuran and stirred at room temperature for 1 hour. A solution of 10mg of 4-formyl-(-)-pimara-9(11),15-diene prepared in the above Example 2 in 1ml of tetrahydrofuran was added thereto and refluxed for 12 hours. The reaction mixture was diluted with 20ml of ethyl acetate, washed with water and brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was then purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 8.3mg of 4-carboethoxyvinyl-(-)-pimara-9(11),15-diene (70%).

^{1}H-NMR(300MHz, $CDCl_3$) : 7.26(d, 1H, J=16.0Hz), 5.75(dd, 1H, J=17.4, 10.7Hz), 5.72(d, 1H, J=16.0Hz), 5.28(m, 1H), 4.86(dd, 1H, J=17.4, 1.4Hz), 4.79(dd, 1H, J=10.7, 1.4Hz), 4.11(q, 2H, J=7.05Hz), 0.65-2.10(m, 19H), 0.93(s, 3H), 0.90(s, 3H), 0.88(s, 3H)

Example 7 : 4-Carboxyvinyl-(-)-pimara-9(11),15-diene

11mg of 4-carboethoxyvinyl-(-)-pimara-9(11),15-diene prepared in the above Example 6 was dissolved in a mixed solution of 1ml of tetrahydrofuran and 1ml of water. 3.9mg of lithium hydroxide was added thereto and refluxed for 12 hours. The reaction mixture was diluted with water, acidified with hydrochloric acid solution (1M), and then extracted with 20ml of ethyl acetate. The organic layer was washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 7.5mg of 4-carboxyvinyl-(-)-pimara-9(11),15-diene (75%).

^{1}H-NMR(300MHz, $CDCl_3$) : 7.37(d, 1H, J=16.1Hz), 5.74(dd, 1H, J=17.5, 10.7Hz), 5.72(d, 1H, J=16.1Hz), 5.29(m, 1H), 4.86(dd, 1H, J=17.4, 1.4Hz), 4.80(dd, 1H, J=10.7, 1.4Hz), 0.71-2.28(m, 16H), 0.95(s, 3H), 0.90(s, 3H), 0.88(s, 3H)

Example 8 : 4-Carbomethoxyethyl-(-)-pimara-9(11),15-diene

10mg of 4-carboethoxyvinyl-(-)-pimara-9(11),15-diene prepared in the above Example 6 was dissolved in 2ml of methanol. 5mg of magnesium powder was added thereto and stirred at room temperature for 12 hours. Hydrochloric acid solution (2M) was added to the reaction mixture to dissolve the remaining magnesium. The reaction mixture was concentrated under reduced pressure and extracted with 20ml of ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 9mg of 4-carbomethoxyethyl-(-)-pimara-9(11),15-diene (90%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.75(dd, 1H, J=17.5, 10.7Hz), 5.30(m, 1H), 4.86(dd, 1H, J=17.4, 1.4Hz), 4.79(dd, 1H, J=10.6, 1.4Hz) 3.59(s, 3H) 0.76-2.17(m, 20H), 1.04(s, 3H), 0.90(s, 3H), 0.77(s, 3H)

Example 9 : 4-Carboxyethyl-(-)-pimara-9(11),15-diene

10mg of 4-carbomethoxyethyl-(-)-pimara-9(11),15-diene prepared in the above Example 8 was dissolved in a mixed solution of 1ml of tetrahydrofuran and 1ml of water. 3.9mg of lithium hydroxide was thereto and refluxed for 12 hours. The reaction mixture was diluted with water, acidified with hydrochloric acid solution (1M), extracted with 20ml of ethyl acetate. The organic layer was washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 6.9mg of 4-carboxyethyl-(-)-pimara-9(11),15-diene (75%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.75(dd, 1H, J=17.5, 10.7Hz), 5.33(m, 1H), 4.86(dd, 1H, J=17.5, 1.4Hz), 4.79(dd, 1H, J=10.7, 1.4Hz), 0.71-2.31(m, 20H) 1.04(s, 3H), 0.90(s, 3H), 0.80(s, 1H)

Example 10 : 4-Chloroformyl-(-)-pimara-9(11),15-diene

To a solution of 10mg of (-)-pimara-9(11),15-diene-4-carboxylic acid in 2ml of benzene, was added 30μl of oxalyl chloride. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure to give unstable 4-chloroformyl-(-)-pimara-9(11),15-diene.

Example 11 : 4-Carbamoyl-(-)-pimara-9(11),15-diene

The reaction mixture prepared in the above Example 10 was distilled under reduced pressure to give a residue, to which 1ml of ammonia solution was added. To the reaction mixture, was added 2ml of ethyl acetate and then stirred at room temperature for 30 minutes. The reaction mixture was extracted with 20ml of ethyl acetate, washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1:3) to afford 9.8mg of 4-carbamoyl-(-)-pimara-

9(11),15-diene (99%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.79(dd, 1H, J=17.5, 10.7Hz), 5.57(s, 1H), 5.38(m, 1H), 4.91(dd, 1H, J=17.5, 1.4Hz), 4.84(dd, 1H, J=10.7, 1.4Hz), 0.79-2.03(m, 16H), 1.26(s, 3H), 1.09(s, 3H), 0.93(s, 3H)

Mass(EI) m/e 301(M+)

Example 12 : 4-(N-methyl)carbamoyl-(-)-pimara-9(11),15-diene

The reaction mixture prepared in the above Example 10 was distilled under reduced pressure to give a residue, to which 1ml of methylamine solution was added. To the reaction mixture, was added 2ml of ethyl acetate and then stirred at room temperature for 30 minutes. The reaction mixture was extracted with 20ml of ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1:3) to afford 10.3mg of 4-(N-methyl)carbamoyl-(-)-pimara-9(11),15-diene (99%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.74(dd, 1H, J=17.3, 10.7Hz), 5.61(s, 1H), 5.31(m, 1H), 4.86(dd, 1H, J=17.4, 1.4Hz), 4.80(dd, 1H, J=10.7, 1.4Hz), 2.71(d, 3H, J=4.86), 0.78-2.12(m, 16H), 1.12(s, 3H), 0.89(s, 3H), 0.88(s, 3H)

Mass(EI) m/e 316(M+)

Example 13 : 4-Carbazoyl-(-)-pimara-9(11),15-diene

The reaction mixture prepared in the above Example 10 was distilled under reduced pressure to give a residue, which was dissolved in 2ml of dry ether. To the reaction mixture, was added 4.5mg of hydrazine monohydrate at room temperature and then stirred at room temperature for 1 hour. The reaction mixture was extracted with 20ml of dichloromethane. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under

reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : dichloromethane/methanol = 30:1) to afford 10.3mg of 4-carbazoyl-(-)-pimara-9(11),15-diene (99%).

^{1}H-NMR(300MHz, $CDCl_3$) : 6.91(s, 1H), 5.74(dd, 1H, J=17.5, 10.7Hz), 5.32(m,1H), 4.86(dd, 1H, J=17.5, 1.5Hz), 4.80(dd, 1H, J=10.7, 1.5Hz), 0.71-2.25(m, 16H), 1.15(s, 3H), 0.92(s, 3H), 0.77(s, 3H)

Mass(EI) m/e 317(M+)

Example 14 : 4-(N-hydroxy)carbamoyl-(-)-pimara-9(11),15-diene

The reaction mixture prepared in the above Example 10 was distilled under reduced pressure to give a residue, to which 1ml of benzene was added. To the reaction mixture, was added 4.5mg of hydroxylamine hydrochloride at 0℃ and then stirred at room temperature for 3 hours. To the reaction mixture, was added 4mg of dry sodium acetate. The reaction mixture was diluted with water and extracted with 20ml of ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1:1) to afford 10.4mg of 4-(N-hydroxy)carbamoyl-(-)-pimara-9(11),15-diene (99%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.72(dd, 1H, J=17.5, 10.7Hz), 5.32(m, 1H), 4.86(d, 1H, J=17.5Hz), 4.80(d, 1H, J=10.7Hz), 0.80-2.24(m, 16H), 1.16(s, 3H), 0.96(s, 3H), 0.88(s, 3H)

Mass(EI) m/e 316(M+)

Example 15 : 16-Hydroxy-(-)-pimara-9(11)-en-4-carboxylic acid

0.6 ml of n-butyllithium (1.6M) was added at -20℃ to a solution of 178mg of (-)-pimara-9(11),15-diene-4-carboxylic acid in 4ml of tetrahydrofuran and stirred for 30 minutes. 0.5ml of borane-methyl sulfide solution (2M) was added to the reaction mixture and then stirred at room

temperature for 26 hours. 0.3ml of sodium hydroxide solution (3N) and 0.3ml of hydrogen peroxide solution (30%) were added to the reaction mixture, which was then stirred at room temperature for 3 hours. The reaction mixture was diluted with 50ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 122.7mg of 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylic acid (68.5%).

IR(neat) : 3401(OH), 2929(CH), 1697(CO) cm^{-1}

^{1}H-NMR(300MHz, $CDCl_3$) : 5.29(m, 1H), 3.67(m, 2H), 0.70-2.15(m, 18H), 1.16(s, 3H), 0.92(s, 3H), 0.87(s, 3H)

Mass(EI) m/e 320(M+)

Example 16 : 16-Hydroxy-(-)-pimara-4-carboxylic acid

45mg of 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylic acid prepared in the above Example 15 was dissolved in 2ml of dry methanol. Catalytic amount of palladium / active carbon (10%) was added thereto, substituted with hydrogen, and stirred at room temperature for 6 hours. The reaction mixture was concentrated under reduced pressure, diluted with diethyl ether, and filtered with silica gel. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 43mg of 16-hydroxy-(-)-pimara-4-carboxylic acid (95%).

^{1}H-NMR(300MHz, $CDCl_3$) : 3.67(m, 2H), 0.69-2.10(m, 20H), 1.19(s, 3H), 0.83(s, 3H), 0.77(s, 3H)

Example 17 : 2'-(Trimethylsilyl)ethyl (-)-pimara-9(11),15-diene-4-carboxylate

The reaction mixture of Example 10 was distilled under reduced pressure to give a residue, to which were added 1ml of pyridine and 0.02ml of trimehtylsilylethanol. The reaction mixture was stirred at room temperature for 20 hours, diluted with 20ml of ethyl acetate, washed with

hydrochloric acid (1M), water and brine. The reaction mixture was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 11.3mg of 2'-(trimethylsilyl)ethyl (-)-pimara-9(11),15-diene-4-carboxylate (85%).

IR(neat) : 1718(CO), 860($Si(CH_3)_3$) cm^{-1}

^{1}H-NMR(300MHz, $CDCl_3$) : 5.77(dd, 1H, J=10.7, 17.6Hz), 5.34(m, 1H), 4.88(dd, 1H, J=1.5, 17.7Hz), 4.82(dd, 1H, J=1.5, 10.6Hz), 4.08(m, 2H), 0.81-2.13(m, 18H), 1.14(s, 3H), 0.91(s, 3H), 0.83(s, 3H), 0.00(s, 9H)

Mass(EI) m/e 402(M+)

Example 18 : 2'-(Trimethylsilyl)ethyl 11,16-dihydroxy-(-)-pimara-4-carboxylate

To a solution of 10mg of 2'-(trimethylsilyl)ethyl (-)-pimara-9(11),15-diene-4-carboxylate prepared in the above Example 17 in 1.5ml of tetrahydrofuran, was added 0.05ml of borane-methyl sulfide (2M) at 0℃. The reaction mixture was stirred at room temperature for 20 hours. 0.1ml of sodium hydroxide solution (3N) and 0.1ml of hydrogen peroxide (30%) were added to the reaction mixture, which was then stirred at room temperature for 3 hours. The reaction mixture was diluted with 20ml of ethyl acetate, washed with water and brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate) to afford 6mg of 2'-(trimethylsilyl)ethyl 11,16-dihydroxy-(-)-pimara-4-carboxylate (55%).

^{1}H-NMR(300MHz, $CDCl_3$) : 4.05(m, 2H), 3.80(dt, 1H, J=4.17, 10.5Hz), 3.68(t, 2H, J=7.5Hz), 0.76-2.17(m, 21H), 1.11(s, 3H), 0.95(s, 3H), 0.86(s, 3H), 0.00(s, 9H)

Example 19 : 11,16-Dihydroxy-(-)-pimara-4-carboxylic acid

To a solution of 6mg of 2'-(trimethylsilyl)ethyl 11,16-dihydroxy-(-)-pimara-4-carboxylate prepared in the above Example 18 in 1ml of

dimethylformamide, was added 0.06ml of tetrabutylammonium fluoride. The reaction mixture was stirred at room temperature for 2 hours, diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate) to afford 4.2mg of 11,16-dihydroxy-(-)-pimara-4-carboxylic acid (91%).

^{1}H-NMR(300MHz, CD_3OD) : 3.76(dt, 1H, J=4.38, 10.71Hz), 3.61(t, 2H, J=7.8Hz), 0.74-2.15(m, 19H), 1.16(s, 3H), 1.08(s, 3H), 0.89(s, 3H)

Mass(EI) m/e 339(M+)

Example 20 : 2'-(Trimethylsilyl)ethyl 13-isoxazolinyl-(-)-pimara-9(11)-en-4-carboxylate

To a solution of 1170mg of N-chlorosuccinimide in 8ml of chloroform, were added 578mg of acetaldoxime and 0.05ml of pyridine. The reaction mixture was stirred at room temperature for 10 minutes. To the reaction mixture, was dropwise added a solution of 194mg of 2'-(trimethylsilyl)ethyl (-)-pimara-9(11),15-diene-4-carboxylate prepared in the above Example 17 in 3ml of chloroform. While stirring the reaction mixture at 40℃, 1.34ml of triethylamine was dropwise added to the reaction mixture for 30 minutes. The reaction mixture was stirred for 20 hours, diluted with 40ml of chloroform, washed with hydrochloric acid solution (1M) and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 162mg of 2'-(trimethylsilyl)ethyl 13-isoxazolinyl-(-)-pimara-9(11)-en-4-carboxylate (73%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.32(m, 1H), 4.19(t, 1H, J=9.9Hz), 4.08(m, 2H), 2.71(m, 2H), 0.74-2.23(m, 18H), 1.92(s, 3H), 1.13(s, 3H), 0.87(s, 3H), 0.79(s, 3H), 0.00(s, 9H)

Example 21 : 13-Isoxazolinyl-(-)-pimara-9(11)-en-4-carboxylic

acid

To a solution of 114mg of 2'-(trimethylsilyl)ethyl 13-isoxazolinyl-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 20 in 7ml of dimethylformamide, was added 0.5ml of tetrabutylammonium fluoride. The reaction mixture was stirred at room temperature for 2 hours, diluted with 50ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/2) to afford 80mg of 13-isoxazolinyl-(-)-pimara-9(11)-en-4-carboxylic acid (90%).

IR(neat) : 1692(CO) cm^{-1}

^{1}H-NMR(300MHz, $CDCl_3$) : 5.35(m, 1H), 4.21(t, 1H, J=10.1Hz), 2.73(m, 2H), 0.77-2.32(m, 16H),

1.94(s, 3H), 1.22(s, 3H), 0.95(s, 3H), 0.81(s, 3H)

Mass(EI) m/e 359(M+)

Example 22: 4-Carboethoxyallyl-(-)-pimara-9(11),15-diene

0.06ml of triethyl phosphonoacetate and 12mg of sodium hydride (60%) were dissolved in 1ml of toluene and stirred for 1 hour. To the reaction mixture, was added a solution of 30mg of 4-formylmethyl-(-)-pimara-9(11),15-diene prepared in the above Example 4 in 1ml of toluene. The reaction mixture was stirred at room temperature for 1 hour, concentrated under reduced pressure to remove toluene, diluted with 20ml of ethyl acetate, washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 28mg of 4-carboethoxyallyl-(-)-pimara-9(11),15-diene (76%).

^{1}H-NMR(300MHz, $CDCl_3$) : 6.94(td, 1H, J=7.8, 15.6Hz), 5.79(m, 2H), 5.34(m, 1H), 4.91(dd, 1H, J=17.4, 1.2Hz), 4.84(dd, J=10.7, 1.2Hz), 4.16(q, 2H, J=7.3Hz), 1.27(t, 3H, J=7.1Hz), 0.80-2.49(m, 18H), 1.08(s, 3H), 0.95(s, 3H), 0.88(s, 3H)

Example 23: 4-Carboxyallyl-(-)-pimara-9(11),15-diene

13mg of 4-carboethoxyallyl-(-)-pimara-9(11),15-diene prepared in the above Example 22 was dissolved in a mixed solution of 1ml of tetrahydrofuran and 1ml of water. 4.4mg of lithium hydroxide monohydrate was added to the reaction mixture, which was refluxed for 12 hours and then diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 10.2mg of 4-carboxyallyl-(-)-pimara-9(11),15-diene (85%).

^{1}H-NMR(300MHz, $CDCl_3$) : 7.02(td, 1H, J=7.8, 15.6Hz), 5.75(m, 2H), 5.30(m, 1H), 4.86(d, 1H, J=17.5Hz), 4.80(d, 1H, J=10.7Hz), 0.69-2.48(m, 18H), 1.04(s, 3H), 0.90(s, 3H), 0.84(s, 3H)

Mass(EI) m/e 342(M^+)

Example 24: 4-Carbomethoxypropyl-(-)-pimara-9(11),15-diene

To a solution of 15mg of 4-carboethoxyallyl-(-)-pimara-9(11),15-diene prepared in the above Example 22 in 2ml of methanol, was added 5mg of magnesium powder. The reaction mixture was stirred at room temperature for 12 hours. Hydrochloric acid solution (2M) was added to the reaction mixture to dissolve the remaining magnesium. The reaction mixture was concentrated under reduced pressure to remove methanol and extracted with 20ml of ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 12mg of 4-carbomethoxypropyl-(-)-pimara-9(11),15-diene (83%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.75(dd, 1H, J=17.5, 10.7Hz), 5.27(m, 1H), 4.86(dd, 1H, J=17.4, 1.2Hz), 4.79(dd, 1H, J=10.7, 1.2Hz), 2.21(dt, 2H,

J=2.0, 7.2Hz), 0.74-1.99(m, 20H), 1.00(s, 3H), 0.90(s, 3H), 0.79(s, 3H)

Example 25: 4-Carboxypropyl-(-)-pimara-9(11),15-diene

10mg of 4-carbomethoxypropyl-(-)-pimara-9(11),15-diene prepared in the above Example 24 was dissolved in a mixed solution of 1ml of tetrahydrofuran and 1ml of water. 3.5mg of lithium hydroxide monohydrate was added to the reaction mixture, which was refluxed for 4 hours and diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 6mg of 4-carboxypropyl-(-)-pimara-9(11),15-diene (62.4%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.80(dd, 1H, J=17.5, 10.7Hz), 5.32(m, 1H), 4.91(dd, 1H, J=17.3, 1.5Hz), 4.84(dd, 1H, J=10.7, 1.5Hz), 0.70-2.35(m, 22H), 1.06(s, 3H), 0.95(s, 3H), 0.84(s, 3H)

Mass(EI) m/e 344(M^+)

Example 26: 4-Hydroxymethylvinyl-(-)-pimara-9(11),15-diene

To a solution of 24mg of 4-carboethoxyvinyl-(-)-pimara-9(11),15-diene prepared in the above Example 6 in 2ml of dichloromethane, was added 0.15ml of diisobutylaluminum hydride solution (1M) at -78℃. After the reaction mixture was stirred for 30 minutes, some drops of methanol was added thereto to terminate the reaction. 20ml of dichloromethane and 20ml of a saturated solution of potassium sodium tartrate tetrahydrate were added to the reaction mixture, which was stirred vigorously at room temperature for 2 hours. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford 20mg of 4-hydroxymethylvinyl-(-)-pimara-9(11),15-diene (95%).

IR(neat) : 3331(OH), 2924(CH) cm^{-1}

Mass(EI) m/e 314(M^+)

Example 27: 4-Formylvinyl-(-)-pimara-9(11),15-diene

20mg of 4-hydroxymethylvinyl-(-)-pimara-9(11),15-diene prepared in the above Example 26, catalytic amount of tetrapropylammonium perruthenate, 12mg of N-methylmorpholine-N-oxide, and molecular sieve powder were dissolved in 2ml of dichloromethane and then stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with diethyl ether, and filtered with silica gel. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 17mg of 4-formylvinyl-(-)-pimara-9(11),15-diene (85.5%).

IR(neat) : 2924(CH), 1691(CO) cm^{-1}

Mass(EI) m/e 312(M^+)

Example 28: 4-Carboethoxybutadienyl-(-)-pimara-9(11),15-diene

69$\mu\ell$ of triethyl phosphonoacetate and 13.4mg of sodium hydride (60%) were dissolved in 1.5ml of tetrahydrofuran and then stirred at room temperature for 1 hour. A solution of 35mg of 4-formylvinyl-(-)-pimara-9(11),15-diene prepared in the above Example 27 in 1ml of tetrahydrofuran was added to the reaction mixture, which was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran, diluted with 20ml of ethyl acetate, washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 41mg of 4-carboethoxybutadienyl-(-)-pimara-9(11),15-diene (95.7%).

^{1}H-NMR(500MHz, $CDCl_3$) : 7.23(dd, 1H, J=15.7, 10.6Hz), 6.39(d, 1H, J=15.7Hz), 6.06(dd, 1H, J=15.6, 10.9Hz), 5.74(m, 2H), 5.29(m, 1H), 4.86(dd, 1H, J=17.5, 1.3Hz), 4.79(dd, 1H, J=10.7, 1.3Hz), 4.13(q, 2H, J=7.14Hz), 0.61-2.24(m, 16H), 1.22(t, 3H, J=5.73Hz), 0.93(s, 3H), 0.91(s, 3H), 0.88(s, 3H)

Example 29: 4-Carboxybutadienyl-(-)-pimara-9(11),15-diene

41mg of 4-carboethoxybutadienyl-(-)-pimara-9(11),15-diene prepared in the above Example 28 was dissolved in a mixed solution of 1ml of tetrahydrofuran and 1ml of water. 13.5mg of lithium hydroxide monohydrate was added to the reaction mixture, which was refluxed for 12 hours and diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 33.5mg of 4-carboxybutadienyl-(-)-pimara-9(11),15-diene (88%).

IR(neat) : 3440(OH), 2920(CH), 1683(CO) cm^{-1}

^{1}H-NMR(500MHz, $CDCl_3$) : 7.39(dd, 1H, J=15.3, 10.8Hz), 6.52(d, 1H, J=15.6Hz), 6.17(dd, 1H, J=15.6, 11.0Hz), 5.81(m, 2H), 5.36(m, 1H), 4.93(dd, 1H, J=17.5, 1.4Hz), 0.68-2.36(m, 16H), 1.00(s, 3H), 0.97(s, 3H), 0.95(s, 3H)

Mass(EI) m/e 354(M^+)

Example 30: 4-Hydroxypropyl-(-)-pimara-9(11),15-diene

To a solution of 40mg of 4-carbomethoxyethyl-(-)-pimara-9(11),15-diene prepared in the above Example 8 in 2ml of dichloromethane, was added 0.25ml of diisobutylaluminum hydride solution (1M) at -78℃. After the reaction mixture was stirred for 30 minutes, some drops of methanol was added thereto to terminate the reaction. 20ml of dichloromethane and 20ml of a saturated solution of potassium sodium tartrate tetrahydrate were added to the reaction mixture, which was vigorously stirred at room temperature for 2 hours. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 36ml of 4-hydroxypropyl-(-)-pimara-9(11),15-diene (98%).

IR(neat) : 3322(OH), 2922(CH) cm^{-1}
Mass(EI) m/e 316(M^+)

Example 31: 4-Formylethyl-(-)-pimara-9(11),15-diene

36mg of 4-hydroxypropyl-(-)-pimara-9(11),15-diene prepared in the above Example 30, catalytic amount of tetrapropylammonium perruthenate, 20mg of N-methylmorpholine-N-oxide, and molecular sieve powder were dissolved in 2ml of dichloromethane and then stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with diethyl ether, and filtered with silica gel. The filtrate was concentrated under reduced pressure to afford 4-formylethyl-(-)-pimara-9(11),15-diene, which was proceeded to the reaction of Example 32.

Example 32: 4-Carboethoxyhomoallyl-(-)-pimara-9(11),15-diene

60$\mu\ell$ of triethyl phosphonoacetate and 12mg of sodium hydride (60%) were dissolved in 1.5ml of tetrahydrofuran and then stirred at room temperature for 1 hour. A solution of 35mg of 4-formylethyl-(-)-pimara-9(11),15-diene prepared in the above Example 31 in 1ml of tetrahydrofuran was added to the reaction mixture, which was stirred at room temperature for 30 minutes. The reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran, diluted with 20ml of ethyl acetate, washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to afford 4-carboethoxyhomoallyl-(-)-pimara-9(11),15-diene, which was proceeded to the reaction of Example 33.

Example 33: 4-Carboxyhomoallyl-(-)-pimara-9(11),15-diene

18mg of 4-carboethoxyhomoallyl-(-)-pimara-9(11),15-diene prepared in the above Example 32 was dissolved in a mixed solution of 1ml of tetrahydrofuran and 1ml of water. 6mg of lithium hydroxide monohydrate was added to the reaction mixture, which was refluxed for 4

hours and diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 13.5mg of 4-carboxyhomoallyl-(-)-pimara-9(11),15-diene (81%).

^{1}H-NMR(300MHz, $CDCl_3$) : 7.03(dtd, 1H, J=2.7, 6.8, 15.6Hz), 5.75(m, 2H), 5.28(m, 1H), 4.86(dd, 1H, J=17.4, 1.2Hz), 4.79(dd, 1H, J=10.6, 1.2Hz), 0.71-2.06(m, 20H), 1.02(s, 3H), 0.90(s, 3H), 0.81(s, 3H)

Mass(EI) m/e 356(M^+)

Example 34: 4-Carbomethoxybutyl-(-)-pimara-9(11),15-diene

To a solution of 18mg of 4-carboethoxyhomoallyl-(-)-pimara-9(11),15-diene prepared in the above Example 32 in 2ml of methanol, was added 5mg of magnesium powder. The reaction mixture was stirred at room temperature for 12 hours. Hydrochloric acid solution (2M) was added to the reaction mixture to dissolve the remaining magnesium. The reaction mixture was concentrated under reduced pressure to remove methanol and extracted with 20ml of ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give 4-carbomethoxybutyl-(-)-pimara-9(11),15-diene, which was proceeded to the reaction of Example 35.

Example 35: 4-Carboxybutyl-(-)-pimara-9(11),15-diene

16mg of 4-carbomethoxybutyl-(-)-pimara-9(11),15-diene prepared in the above Example 34 was dissolved in a mixed solution of 1ml of tetrahydrofuran and 1ml of water. 5mg of lithium hydroxide monohydrate was added to the reaction mixture, which was refluxed for 4 hours and diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl

acetate/hexane = 1/3) to afford 14.5mg of 4-carboxybutyl-(-)-pimara-9(11),15-diene (94%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.75(dd, 1H, J=17.5, 10,7Hz), 5.27(m, 1H), 4.86(dd, 1H, J=17.4, 1.4Hz), 4.79(dd, 1H, J=10.7, 1.4Hz), 2.29(dt, 2H, J=2.4, 7.4Hz), 0.68-1.98(m, 22H), 1.01(s, 3H), 0.90(s, 3H), 0.76(s, 3H)

Mass(EI) m/e 358(M^+)

Example 36 : Pipsylamide

2ml of ammonia solution was added to 15mg of pipsyl chloride and then stirred at room temperature for 5 minutes. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give 11.2mg of pipsylamide (80%) as a white solid form.

IR(neat) : 3351(NH), 816(CI) cm^{-1}

^{1}H-NMR(300MHz, $CDCl_3$) : 7.81(d, 2H, J=8.28), 7.57(d, 2H, J=8.04Hz), 4.74(s, 1H)

Mass(EI) m/e 283(M+)

Example 37: 4-Chloroformylmethyl-(-)-pimara-9(11),15-diene

To a solution of 10mg of 4-carboxymethyl-(-)-pimara-9(11),15-diene prepared in the above Example 5 in 2ml of benzene, was added 30 $\mu\ell$ of oxalyl chloride. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure to give unstable 4-chloroformylmethyl-(-)-pimara-9(11),15-diene.

Example 38: 4-(N-pipsyl)carbamoylmethyl-(-)-pimara-9(11),15-diene

9.6mg of pipsylamide prepared in the above Example 36 and 1.4mg of sodium hydride (60%) were dissolved in 1ml of tetrahydrofuran and stirred at room temperature for 30 minutes (Reaction Mixture A). The reaction mixture prepared in the above Example 37 was concentrated

under reduced pressure to give a residue, which was then dissolved in 1ml of tetrahydrofuran (Reaction Mixture B). Reaction Mixture B was added to Reaction Mixture A and stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran, diluted with 20ml of dichloromethane, washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1:5) to afford 17mg of 4-(N-pipsyl)carbamoylmethyl-(-)-pimara-9(11),15-diene (92%).

IR(neat) : 3434(NH), 2922(CH), 1715(CO) cm^{-1}

^{1}H-NMR(300MHz, $CDCl_3$) : 7.84(d, 2H, J=8.8Hz), 7.69(d, 2H, J=8.5Hz), 5.73(dd, 1H, J=17.5, 10.7Hz), 5.29(m, 1H), 4.85(d, 1H, J=17.5Hz), 4.79(d, 1H, J=10.5), 0.82-2.36(m, 18H), 0.91(s, 3H), 0.88(s, 3H), 0.85(s, 3H)

Mass(EI) m/e 581(M^+)

Example 39: 4-Chloroformylethyl-(-)-pimara-9(11),15-diene

To a solution of 10mg of 4-carboxyethyl-(-)-pimara-9(11),15-diene prepared in the above Example 9 in 2ml of benzene, was added 30$\mu\ell$ of oxalyl chloride. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure to give unstable 4-chloroformylethyl-(-)-pimara-9(11),15-diene.

Example 40: 4-(N-pipsyl)carbamoylethyl-(-)-pimara-9(11),15-diene

9.6mg of pipsylamide prepared in the above Example 36 and 1.4mg of sodium hydride (60%) were dissolved in 1ml of tetrahydrofuran and stirred at room temperature for 30 minutes (Reaction Mixture A). The reaction mixture prepared in the above Example 39 was concentrated under reduced pressure to give a residue, which was then dissolved in 1ml of tetrahydrofuran (Reaction Mixture B). Reaction Mixture B was added to Reaction Mixture A and stirred at room temperature for 1 hour. The

reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran, diluted with 20ml of dichloromethane, washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1:5) to afford 16.2mg of 4-(N-pipsyl)carbamoylethyl-(-)-pimara-9(11),15-diene (90%).

^{1}H-NMR(300MHz, $CDCl_3$) : 8.21(s, 1H), 7.85(d, 2H, J=8.5Hz), 7.71(d, 2H, J=8.5Hz), 5.74(dd, 1H, J=17.4, 10.4Hz), 5.27(m, 1H), 4.85(dd, 1H, J=17.4, 1.2Hz), 4.79(dd, 1H, J=10.7, 1.2Hz), 0.64-2.20(m, 20H), 0.98(s, 3H), 0.88(s, 3H), 0.70(s, 3H)

Mass(EI) m/e 595(M^+)

Example 41: 4-(N-methanesulfonyl)carbamoylethyl-(-)-pimara-9(11),15-diene

6mg of methanesulfonamide and 2.5mg of sodium hydride (60%) were dissolved in 1ml of tetrahydrofuran and stirred at room temperature for 30 minutes (Reaction Mixture A). The reaction mixture prepared in the above Example 39 was concentrated under reduced pressure to give a residue, which was then dissolved in 1ml of tetrahydrofuran (Reaction Mixture B). Reaction Mixture B was added to Reaction Mixture A and stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran, diluted with 20ml of ethylacetate, washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1:3) to afford 9.2mg of 4-(N-methanesulfonyl)carbamoylethyl-(-)-pimara-9(11),15-diene (75%).

^{1}H-NMR(300MHz, $CDCl_3$) : 8.34(s, 1H), 5.75(dd, 1H, J=17.4, 10.7Hz), 5.29(m, 1H), 4.86(d, 1H, J=17.4Hz), 4.79(d, 1H, J=10.6Hz), 3.24(s, 3H), 0.77-2.29(m, 20H), 1.04(s, 3H), 0.90(s, 3H), 0.78(s, 3H)

Example 42: 4-Chloroformylbutadienyl-(-)-pimara-9(11),15-diene

To a solution of 12mg of 4-carboxybutadienyl-(-)-pimara-9(11),15-diene prepared in the above Example 29 in 2ml of benzene, was added 30 $\mu\ell$ of oxalyl chloride. The reaction mixture was stirred at room temperature for 1 hour and concentrated under reduced pressure to give unstable 4-chloroformylbutadienyl-(-)-pimara-9(11), 15-diene.

Example 43: 4-(N-pipsyl)carbamoylbutadienyl-(-)-pimara-9(11),15-diene

9.6mg of pipsylamide prepared in the above Example 36 and 1.4mg of sodium hydride (60%) were dissolved in 1ml of tetrahydrofuran and stirred at room temperature for 30 minutes (Reaction Mixture A). The reaction mixture prepared in the above Example 42 was concentrated under reduced pressure to give a residue, which was then dissolved in 1ml of tetrahydrofuran (Reaction Mixture B). Reaction Mixture B was added to Reaction Mixture A and stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran, diluted with 20ml of dichloromethane, washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1:3) to afford 10mg of 4-(N-pipsyl)carbamoylbutadienyl-(-)-pimara-9(11),15-diene (48%).

^{1}H-NMR(300MHz, $CDCl_3$) : 8.41(s, 1H), 7.83(d, 2H, J=8.5Hz), 7.72(d, 2H, J=8.3Hz), 7.26(m, 1H), 6.47(d, 1H, J=15.6Hz), 6.04(dd, 1H, J=15.6, 10.7Hz), 5.71(m, 2H), 5.28(m, 1H), 5.28(m, 1H), 4.86(dd, 1H, J=17.4, 1.2Hz), 4.79(dd, 1H, J=10.7, 1.2Hz), 0.71-2.25(m, 16H), 0.90(s, 3H), 0.89(s, 3H), 0.81(s, 3H)

Mass(EI) m/e 619(M^+)

Example 44: 2'-(Trimethylsilyl)ethyl 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylate

To a solution of 73mg of 2'-(trimethylsilyl)ethyl (-)-pimara-9(11),15-diene-4-carboxylate prepared in the above Example 17 in 5ml of tetrahydrofuran, was added 0.33ml of borane-methyl sulfide solution (2M) at 0℃. The reaction mixture was stirred at 0℃ for 60 hours. 0.3ml of sodium hydroxide solution (3N) and 0.3ml of hydrogen peroxide (30%) were added to the reaction mixture, which was then stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure to remove tetrahydrofuran, diluted with 20ml of ethyl acetate, washed with water and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/5) to afford 24mg of 2'-(trimethylsilyl)ethyl 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylate (32%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.30(m, 1H), 4.08(m, 2H), 3.69(m, 2H), 0.78-2.25(m, 20H), 1.13(s, 3H), 0.87(s, 3H), 0.83(s, 3H), 0.00(s, 9H)

Example 45: 2'-(Trimethylsilyl)ethyl 16-methoxy-(-)-pimara-9(11)-en-4-carboxylate

1.8ml of diethyl ether and 0.2ml of dimethylsulfoxide were added to 2.5mg of sodium hydride (60%). While stirring the reaction mixture at room temperature, a solution of 13mg of 2'-(trimethylsilyl)ethyl 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 44 in 0.5ml of diethyl ether was added thereto. After 30 minutes, 10$\mu\ell$ of iodomethane was added to the reaction mixture, which was stirred for 2 hours. The reaction mixture was diluted with 20ml of diethyl ether, washed with water and brine, dried over magnesium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 10mg of 2'-(trimethylsilyl)ethyl 16-methoxy-(-)-pimara-9(11)-en-4-carboxylate (74%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.30(m, 1H), 4.08(m, 2H), 3.40(m, 2H), 3.28(s, 3H), 0.78-2.17(m, 20H), 1.13(s, 3H), 0.87(s, 3H), 0.82(s, 3H),

0.00(s, 9H)

Example 46: 16-Methoxy-(-)-pimara-9(11)-en-4-carboxylic acid

To a solution of 20mg of 2'-(trimethylsilyl)ethyl 16-methoxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 45 in 1ml of dimethylsulfoxide, was added 0.15ml of tetrabutylammonium fluoride solution (1M). The reaction mixture was stirred at room temperature for 10 minutes, diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/8) to afford 12mg of 16-methoxy-(-)-pimara-9(11)-en-4-carboxylic acid (78%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.29(m, 1H), 3.38(m, 2H), 3.25(s, 3H), 0.58-2.19(m, 18H), 1.17(s, 3H), 0.91(s, 3H), 0.79(s, 3H)

Mass(EI) m/e 334(M^+)

Example 47: 2'-(Trimethylsilyl)ethyl 16-acetyloxy-(-)-pimara-9(11)-en-4-carboxylate

23mg of 2'-(trimethylsilyl)ethyl 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 44 was dissolved in 2ml of pyridine. 20$\mu\ell$ of acetic anhydride was added to the reaction mixture, which was then stirred at room temperature for 3 hours. 1ml of water was added to the reaction mixture, which was stirred for 20 minutes, diluted with 20ml of ethyl acetate, and then washed with a saturated solution of sodium carbonate, hydrochloric acid solution (0.5M), and brine. The reaction mixture was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 21mg of 2'-(trimethylsilyl)ethyl 16-acetyloxy-(-)-pimara-9(11)-en-4-carboxylate (83%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.30(m, 1H), 4.08(m, 4H), 0,73-2.22(m, 20H), 1.99(s, 3H), 1.13(s, 3H), 0.87(s, 3H), 0.84(s, 3H), 0.00(s,

9H)

Example 48: 16-Acetyloxy-(-)-pimara-9(11)-en-4-carboxylic acid

To a solution of 21mg of 2'-(trimethylsilyl)ethyl 16-acetyloxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 47 in 1ml of dimethylsulfoxide, was added 0.15ml of tetrabutylammonium fluoride solution (1M). The reaction mixture was stirred at room temperature for 30 minutes, diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine. The reaction mixture was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/8) to afford 14mg of 16-acetyloxy-(-)-pimara-9(11)-en-4-carboxylic acid (82%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.28(m, 1H), 4.08(t, 2H, J=7.8Hz), 0.68-2.21(m, 18H), 1.97(s, 3H), 1.17(s, 3H), 0.92(s, 3H), 0.82(s, 3H)

Mass(EI) m/e 362(m^+)

Example 49: 2'-(Trimethylsilyl)ethyl 16-methoxymethoxy-(-)-pimara-9(11)-en-4-carboxylate

To a solution of 15mg of 2'-(trimethylsilyl)ethyl 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 44 in 2ml of dichloromethane, were added 13$\mu\ell$ of diisopropylethylamine and 6$\mu\ell$ of methoxymethyl chloride. The reaction mixture was stirred at room temperature for 1 hour, diluted with 20ml of dichloromethane, and washed with a saturated solution of ammonium chloride, water and brine. The reaction mixture was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was then was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/30) to afford 11.5mg of 2'-(trimethylsilyl)ethyl 16-methoxymethoxy-(-)-pimara-9(11)-en-4-carboxylate (69%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.30(m, 1H), 4.08(t, 2H, J=7.8Hz), 4.08(m, 2H), 3.55(dt, 2H, J=2.9, 7.5Hz), 3.32(s, 3H), 0.78-2.25(m, 20H),

1.13(s, 3H), 0.87(s, 3H), 0.83(s, 3H) 0.00(s, 9H)

Example 50: 16-Methoxymethoxy-(-)-pimara-9(11)-en-4-carboxylic acid

To a solution of 22.5mg of 2'-(trimethylsilyl)ethyl 16-methoxymethoxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 49 in 1ml of dimethylsulfoxide, was added 0.15ml of tetrabutylammonium fluoride solution (1M). The reaction mixture was stirred at room temperature for 1 hour, diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine. The reaction mixture was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/5) to afford 14mg of 16-methoxymethoxy-(-)-pimara-9(11)-en-4-carboxylic acid (76%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.29(m, 1H), 4.55(s, 2H), 3.53(dt, 2H, J=2.9, 7.5Hz), 3.29(s, 3H), 0.74-2.24(m, 18H), 1.17(s, 3H), 0.91(s, 3H), 0.80(s, 3H)

Mass(EI) m/e 364(M^+)

Example 51: 2'-(Trimethylsilyl)ethyl 16-methoxyethoxymethoxy-(-)-pimara-9(11)-en-4-carboxylate

To a solution of 18mg of 2'-(trimethylsilyl)ethyl 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 44 in 2ml of dichloromethane, were added 16$\mu\ell$ of diisopropylethylamine and 10$\mu\ell$ of methoxyethoxymethyl chloride. The reaction mixture was stirred at room temperature for 2 hours, diluted with 20ml of dichloromethane, and washed with a saturated solution of ammonium chloride, water and brine. The reaction mixture was dried over magnesium sulfate and filtered. The filtrate was concentrated under reduced pressure to give a residue, which was then was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/10) to afford 14.5mg of 2'-(trimethylsilyl)ethyl 16-methoxyethoxymethoxy-(-)-pimara-9(11)-en-4-carboxylate (66%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.30(m, 1H), 4.66(s, 2H), 4.08(m, 2H), 3.59(m, 6H), 3.36(s, 3H), 0.72-2.24(m, 20H), 1.13(s, 3H), 0.87(s, 3H), 0.82(s, 3H), 0.00(s, 9H).

Example 52: 16-Methoxyethoxymethoxy-(-)-pimara-9(11)-en-4-carboxylic acid

To a solution of 14.5mg of 2'-(trimethylsilyl)ethyl 16-methoxyethoxymethoxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 51 in 1ml of dimethylsulfoxide, was added 0.1ml of tetrabutylammonium fluoride solution (1M). The reaction mixture was stirred at room temperature for 1 hour, diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/3) to afford 11mg of 16-methoxyethoxymethoxy-(-)-pimara-9(11)-en-4-carboxylic acid (91%).

^{1}H-NMR(300MHz, $CDCl_3$) : 5.28(m, 1H), 4.64(s, 2H), 3.56(m, 6H), 3.33(s, 3H), 0.76-2.20(m, 18H), 1.17(s, 3H), 0.91(s, 3H), 0.80(s, 3H),

Mass(EI) m/e 333(M^+-methoxyethoxy)

Example 53: 2'-(Trimethylsilyl)ethyl 15-formyl-(-)-pimara-9(11)-en-4-carboxylate

27.7mg of 2'-(trimethylsilyl)ethyl 16-hydroxy-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 44, catalytic amount of tetrapropylammonium perruthenate, 12.5mg of N-methylmorpholine-N-oxide, and molecular sieve powder were dissolved in 2ml of dichloromethane and then stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, diluted with diethyl ether, and filtered with silica gel. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/20) to afford

27mg of 2'-(trimethylsilyl)ethyl 15-formyl-(-)-pimara-9(11)-en-4-carboxylate (98%).

^{1}H-NMR(400MHz, $CDCl_3$) : 9.83(m, 1H), 5.31(m, 1H), 4.07(m, 2H), 0.71-2.40(m, 20H), 1.13(s, 3H), 0.99(s, 3H), 0.88(s, 3H), 0.00(s, 9H)

Example 54: 2'-(Trimethylsilyl)ethyl 16-methoxyimino-(-)-pimara-9(11)-en-4-carboxylate

30mg of 2'-(trimethylsilyl)ethyl 15-formyl-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 53 was dissolved in 1.5ml of pyridine. 32mg of methoxylamine hydrochloride was added to the reaction mixture, which was then stirred at room temperature for 20 hours. The reaction mixture was concentrated under reduced pressure, diluted with diethyl ether, and filtered with silica gel. The filtrate was concentrated under reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/20) to afford 29mg of 2'-(trimethylsilyl)ethyl 16-methoxyimino-(-)-pimara-9(11)-en-4-carboxylate (90%, trans:cis=2:1).

trans isomer ^{1}H-NMR(400MHz, $CDCl_3$) : 7.39(t, 1H, J=6.9Hz), 5.31(m, 1H), 4.08(m, 2H), 3.79(s, 3H), 0.75-2.25(m, 20H), 1.13(s, 3H), 0.87(s, 3H), 0.85(s, 3H), 0.00(s, 9H)

cis isomer ^{1}H-NMR(400MHz, $CDCl_3$) : 6.70(t, 1H, J=5.7Hz), 5.31(m, 1H), 4.08(m, 2H), 3.81(s, 3H), 0.75-2.25(m, 20H), 1.13(s, 3H), 0.87(s, 3H), 0.85(s, 3H), 0.00(s, 9H)

Example 55: 16-Methoxyimino-(-)-pimara-9(11)-en-4-carboxylic acid

To a solution of 29mg of 2'-(trimethylsilyl)ethyl 16-methoxyimino-(-)-pimara-9(11)-en-4-carboxylate prepared in the above Example 54 in 1ml of dimethylsulfoxide, was added 0.2ml of tetrabutylammonium fluoride solution (1M). The reaction mixture was stirred at room temperature for 1 hour, diluted with 20ml of ethyl acetate, washed with hydrochloric acid solution (0.5M) and brine, dried over magnesium sulfate, and then filtered. The filtrate was concentrated under

reduced pressure to give a residue, which was purified by silica gel column chromatography (eluent : ethyl acetate/hexane = 1/8) to afford 21mg of 16-methoxyimino-(-)-pimara-9(11)-en-4-carboxylic acid (90%, trans : cis = 2:1).

trans isomer ^{1}H-NMR(400MHz, $CDCl_3$) : 7.36(t, 1H, J=6.9Hz), 5.29(m, 1H), 3.76(s, 3H), 0.70-2.24(m, 18H), 1.17(s, 3H), 0.91(s, 3H), 0.83(s, 3H)

cis isomer ^{1}H-NMR(400MHz, $CDCl_3$) : 6.68(t, 1H, J=5.7Hz), 5.29(m, 1H), 3.79(s, 3H), 0.70-2.24(m, 18H), 1.17(s, 3H), 0.91(s, 3H), 0.83(s, 3H)

Mass(EI) m/e 347(M^+)

Experimental example 1. Inhibition effect of natural single material and synthetic derivatives thereof against PGE_2 synthesis

The inhibition effect of the novel derivatives against PGE2 synthesis was tested *in vitro*. The said inhibition effect is brought on by inhibiting cyclooxygenase-2 activity. The novel derivatives were synthesized from (-)-pimara-9(11), 15-diene-4-carboxylic acid, which is a diterpene compound isolated from root-bark of Acanthopanax Koreanum.

The testing process was as follows:

3 Unit of COX-2 (Layman chemical) that is separated from sheep placenta and purified was mixed with 1.0 mM of hematin, 1.95 mM of 1-epineprine and 0.49 mM of reduced glutathion, all as a cofactor. The mixture was standed on ice for 5 min. To the mixture, the sample for assay of COX-2 activity was added, and then incubated on ice for 10 min. After preincubation, 0.02 μCi of [1-^{14}C] arachidonic acid, as an substrate, was added, and reacted at 37°C for 20 min. For the termination of the reaction, 10 μl of 2 M HCl was added. Prostaglandin produced was extracted with ethylether twice. Two ethylether layers were integrated, and the solvent was evaporated at a 37°C water-bath. The concentrate was dissolved in acetone, loaded at TLC plate, and then developed with a mixed solvent of $CHCl_3$: MeOH : acetic acid (18:1:1). PGE_2 part of TLC plate developed was observed using autoradiography (PACKARD). The amount of PGE_2

decreased by the sample was compared with reference, and then COX-2 inhibition activity of the sample was determined.

The test result was showed in the following Table 1. IC_{50} is the concentration of test sample that can inhibit 50% of PGE_2 activity.

Table 1. Inhibition effect of natural single material and synthetic derivatives thereof against PGE_2 synthesis, the said inhibition effect brought on by inhibiting of COX-2 activity.

Teas Samples					IC_{50}
Material	R_4	R_1	R_2	R_3	(μM)
Natural Component	-				790.4
Aspirin	-				33865.7
Indometh-acin	-				82.0
NS-398	-				38.4
Example 1	CH_2OH	Double bond	Double bond	Vinyl	>2000
Example 5	CHCHCOOH	Double bond	Double bond	Vinyl	82.3
Example 7	CH CHCOOH	Double bond	Double bond	Vinyl	69.7
Example 9	CH_2 CH_2COOH	Double bond	Double bond	Vinyl	105.0
Example 11	$CONH_2$	Double bond	Double bond	Vinyl	>2000
Example 12	$CONHCH_2$	Double bond	Double bond	Vinyl	>2000
Example 13	$CONHNH_2$	Double bond	Double bond	Vinyl	41.9
Example 14	CONHOH	Double bond	Double bond	Vinyl	818.9
Example 15	CO_2H	Double bond	Double bond	CH_2CH_2OH	>2000
Example 19	CO_2H	OH	H	CH_2CH_2OH	>2000
Example 21	CO_2H	Double	Double	Isoxazoliny	>2000

		bond	bond		
Example 23	$CH_2CHCHCO_2H$	Double bond	Double bond	Vinyl	32.0
Example 25	$CH_2CH_2CH_2CO_2H$	Double bond	Double bond	Vinyl	49.4
Example 29	$CHCHCHCHCO_2H$	Double bond	Double bond	Vinyl	26.8
Example 33	$CH_2CH_2CHCHCO_2H$	Double bond	Double bond	Vinyl	63.8
Example 35	$CH_2CH_2CH_2CH_2CO_2H$	Double bond	Double bond	Vinyl	38.7
Example 38	$CH_2CONHSO_2PhI$	Double bond	Double bond	Vinyl	72.2
Example 40	CH_2 $CH_2CONHSO_2PhI$	Double bond	Double bond	Vinyl	60.7
Example 41	CH_2 $CH_2CONHSO_2Me$	Double bond	Double bond	Vinyl	179.8
Example 43	$CHCHCHCHCONHSO_2PhI$	Double bond	Double bond	Vinyl	25.6
Example 46	CO_2H	Double bond	Double bond	CH_2CH_2OMe	>2000
Example 48	CO_2H	Double bond	Double bond	CH_2CH_2OAc	1420
Example 50	CO_2H	Double bond	Double bond	CH_2CH_2OMOM	>2000
Example 52	CO_2H	Double bond	Double bond	CH_2CH_2OMeM	>2000
Example 55	CO_2H	Double bond	Double bond	$CH_2CHNOCH_3$	>2000

In the above test result, the compound according to the present invention can show the 50% inhibition effect of PGE_2 synthesis only at 26 μM of its concentration minimally while indomethacin, which is a conventional anti-inflammatory analgesic agent, needs the concentration of about 84 μM for the said effect. Therefore, it is ascertained that the compound according to the present invention has the anti-inflammatory activity increased at max 3.2 times, compared to indomethacin. Compared

with NS-398 [Prostaglandins Vol.47, p55(1994) and Gen. Pharmac. Vol.24, No.1 pp105-110(1993)] of Taisho Pharmaceutical Company, the compound according to the present invention showed the powerful activity 1.5 times. It is generally known that the said NS-398 has the excellent selective inhibition effect of COX-2 against COX-1.

Experimental example 2. Anti-inflammatory activity of natural single material and synthetic derivatives thereof against acute inflammation

For some of the natural single material and synthetic derivatives thereof, of which the inhibition effect against PGE2 synthesis was tested in Experimental example 1, the anti-inflammatory activity against arthritis was tested using a mono-arthritis model as follows:

(A) Administration of derivatives and induction of arthritis

Derivatives synthesized were dissolved in the mixed solvent of ethanol : Tween 80 : saline (1:1:8), and then administered by intraperitoneal injection. Referring to the result of the in vitro test, 5 mg/kg was used as a dose for primary screening test. Adjuvant that was dissolved in mineral oil and then sterilized, was administered into tibeo-calcanean joint of right crus posterius of rat to induce arthritis. The injection volume is controlled to be contained M. butyricum 100 μg/50 μl.

(B) Determination of effect of derivatives

Edema degree was determined primarily, and the degree was used as an index of inflammation. The degree was determined by the estimation method for section area of tibeo-calcanean joint part. Width and length measurements of the joint part were taken according to time schedule upon inducing inflammation, and the width multiplied by the length. The multiplied value was then used as a section area index (SAI). On the basis of the section area index, edema index was calculated as follows:

(SAI of inflammatory joint – SAI of normal joint)

$$\text{Edema Index (\%)} = \frac{\text{SAI of normal joint}}{\text{SAI of normal joint}} \times 100$$

Each index was determined at 1, 4 and 24 hours after adjuvant injection. The index value determined at the same part before adjuvant injection was used as one of normal joint.

Unpaired t-test or ANOVA using Fisher PLSD verified the statistical significance.

(C) Test result of anti-inflammation

For diterpene derivatives of formula 5, 7, 8 and 18, which have excellent inhibition effect against PGE_2 synthesis, *in vivo* activity against single arthritis was tested using koprofen and indomethacin as a reference drug.

The derivatives of formula 5 and 7 showed the effect of decreasing the edema index size to be not more then half at 1 hour after inducing inflammation. That effect is more excellent than those of koprofen and indometacin. The said derivatives showed an even superior effect, also after 4 hours, then koprofen or indometacin does.

Experimental example 3. Test of cytotoxicity of derivatives synthesized from natural single material

To investigate the utility of diterpene derivatives synthesized, cytotoxicities of some derivatives were tested.

The cytotoxicity was tested using Raw 264.7. The cytotoxicity and non-cytotoxicity were judged by performing MTT assay at 48 hours after sample treatment.

The test result was given in the following Table 2.

Table 2. Test of cytotoxicity of derivatives synthesized from natural single material.

Teas Samples	IC_{50} (mM)

Material name	R_4	R_1	R_2	R_3	
Example 5	CHCHCOOH	double bond	double bond	Vinyl	0.1395
Example 7	CH CHCOOH	double bond	double bond	Vinyl	0.1390
Example 9	CH_2 CH_2COOH	double bond	double bond	Vinyl	0.1145
Example 15	CO_2H	double bond	double bond	CH_2CH_2OH	0.1390
Example 16	CO_2H	H_2	H	CH_2CH_2OH	0.1370
Example 19	CO_2H	OH	H	CH_2CH_2OH	0.1515
Example 21	CO_2H	double bond	double bond	Isoxazoliny	0.2500

In the test result of cytotoxicity, each derivative mostly showed a low cytotoxicity. Therefore, it is clear that the derivatives synthesized can be used as a medicine, that is, anti-inflammatory analgesic agent.

Pharmaceutical preparation example

1. Preparation of tablet

Compound of Example 35	2.5 mg
Lactose BP	151.0 mg
Starch BP	30.0 mg
Pregelatinized corn starch BP	15.0 mg

Compound of Example 35 was sieved, mixed with lactose, starch and pregelatinized corn starch. To the mixture, purified water was added. The paste was granulated, dried, mixed with magnesium stearate, and then compressed to obtain tablet.

2. Preparation of injection (anticancer agent)

Compound of Example 35	800 μg
d-HCl	to be pH 3.5
Saline for Injection BP	maximum 1 ml

Compound of Example 35 was dissolved in proper volume of

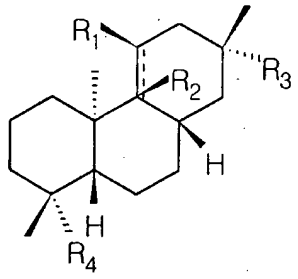
saline for injection BP. The pH of the resultant solution was controlled with d-HCl BP to be pH 3.5, and then its volume was controlled with saline for Injection BP. The solution mixed completely was filled in 5-ml type 1 ample maken of glass. The top of ample was fused for sealing. The solution contained in ample was autoclaved at 120°C for 15 min to be sterilized and to obtain an injection.

Industrial Applicability

The present invention confirmed the fact that the effect of inhibiting PGE_2 synthesis in vitro of novel derivatives of the present invention, which are synthesized according to the process of the present invention from (-)-pimara-9(11),15-diene-4-carboxylic acid of Chemical Formula 2, a diterpene compound isolated from root-bark and bark of Acanthopanax Koreanum, is superior to indomethacin, and these compounds have 3.2-fold physiological activity of anti-inflammatory action. These compounds also showed excellent effect in anti-inflammatory experiments using animal models with low toxicity. Thus, the diterpene component of Acanthopanax Koreanum and synthetic derivatives thereof can be usefully employed as an anti-inflammatory analgesic agent.

CLAIMS

1. A diterpene derivative represented by Chemical Formula 1:



1

wherein, R_1 and R_2 individually represent hydrogen or hydroxy, or they form a double bond in the cycle, R_3 represents vinyl, hydroxyethyl, methoxyethyl, acetyloxyethyl, methoxymethoxyethyl, methoxyethoxymethoxyethyl, methoxyiminoethyl or isoxazolinyl group, R_4 represents hydroxymethyl, carboxyl, carboxymethyl, carboxyvinyl, carboxyethyl, carboxypropyl, carboxybutyl, carboxybutadienyl, carboxyallyl, carboxyhomoallyl, carbamoyl, methylcarbamoyl, hydroxycarbamoyl, carbazoyl, N-pipsylcarbamoylmethyl, N-pipsylcarbamoylethyl, N-pipsylcarbamoylbutadienyl or N-methanesulfonylcarbamoylethyl group.

2. An anti-inflammatory analgesic agent comprising the diterpene derivative according to claim 1 as an active ingredient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00038

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 C 63/44, 57/40, 233/00, 311/00; A 61 K 31/19, 31/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 C 63/44, 57/40, 233/00, 311/00; A 61 K 31/19, 31/16

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

QUESTEL:G-DARC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/34 300 A1 (KOREA INSTITUTE OF SCIENCE AND TECHNOLOGY) 21 December 1995 (21.12.95), claims.	1,2
X	Chemical abstracts, Vol.127, No.1, 07 July 1997 (Columbus, Ohio, USA), page 594, abstract No.5280z, F.G.CRUZ et al. "Relative stereochemistry determination of primaradienes through oxidation products", Ouim Nora 1997, 20(3), 261-266.	1
X	Chemical abstracts, Vol.116, No.11, 16 March 1992 (Columbus, Ohio, USA), page 411, abstract No.102659c, C.M.CHAMY et al. "Diterpenoids from Calceolaria species. Part 10. Diterpenes from Calceolaria polifolia" Phytochemistry 1991, 30(10), 3365-8.	1
X	Chemical abstracts, Vol.114, No.3, 21 January 1991 (Columbus, Ohio, USA), page 408, abstract No. 20960p, C.M.CHAMY et al. "Diterpenoids from Calceolaria species Part. 5. Diterpenes from Calceolaria lepida", Phytochemistry 1990, 29(9), 2943-6.	1

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
„A" document defining the general state of the art which is not considered to be of particular relevance
„E" earlier application or patent but published on or after the international filing date
„L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
„O" document referring to an oral disclosure, use, exhibition or other means
„P" document published prior to the international filing date but later than the priority date claimed
„T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
„X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
„Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 June 1999 (08.06.99)	16 June 1999 (16.06.99)
Name and mailing adress of the ISA/AT Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hofbauer Telephone No. 1/53424/225

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00038

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Chemcial abstracts, Vol. 77, No.15. 09 October 1972 (Columbus, Ohio, USA), page 193, abstract No. 98751h, V.K.MOROZKOV et al. "Neutral fraction of the oleoresin of Pinus sylvestris 3. Norditerpene compounds", Izv. Sib. Otd. Akad Nauk SSSR, Ser. Khim. Nauk 1972, (1), 128-34.	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 99/00038

In Recherchenbericht angeführtes Patentdokument Patent document cited in search report Document de brevet cité dans le rapport de recherche	Datum der Veröffentlichung Publication date Date de publication	Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets	Datum der Veröffentlichung Publication date Date de publication
WO A1 9534300	21-12-1995	CN A 1150758	28-05-1997
		JP T2 10501549	10-02-1998
		KR B1 145941	17-08-1998
		EP A1 759751	05-03-1997